Lipase-Mediated Synthesis of Enantiopure *N*-Carbobenzoxy-3-hydroxy-1,2,3,4-tetrahydro- and *N*-Carbobenzoxy-3-hydroxy-1,2,3,6-tetrahydropyridines from 3-Hydroxypyridine

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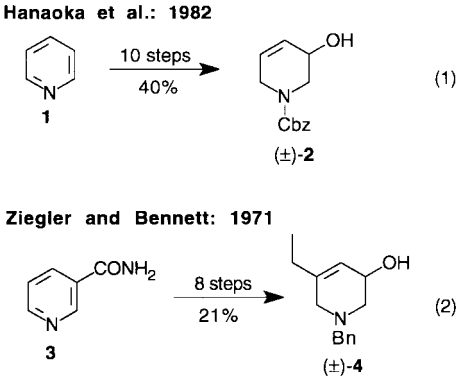
Abstract: Two isomeric chiral hydroxytetrahydropyridines, having high potential utility for the construction of a variety of chiral amine derivatives, have been prepared in both enantiomeric forms by employing lipase-mediated resolution starting from 3-hydroxypyridine. Thus, on exposure to sodium borohydride in the presence of carbobenzoxy chloride, 3-hydroxypyridine has been found to furnish racemic *N*-carbobenzoxy-3-hydroxy-1,2,3,4-tetrahydropyridine, which is resolved under trans-esterification conditions in the presence of lipase PS to give both enantiomeric products in enantiopure forms. Isomerization of the chiral 1,2,3,4-tetrahydro-product into the chiral 1,2,3,6-tetrahydro-derivative has been accomplished without loss of the original chiral integrity. The racemic 1,2,3,6-tetrahydro-derivative has also been resolved under the same lipase-mediated trans-esterification conditions.

Key words: Lipase-mediated kinetic resolution, trans-esterification, chiral building block, tetrahydropyridinol, regioselective reduction



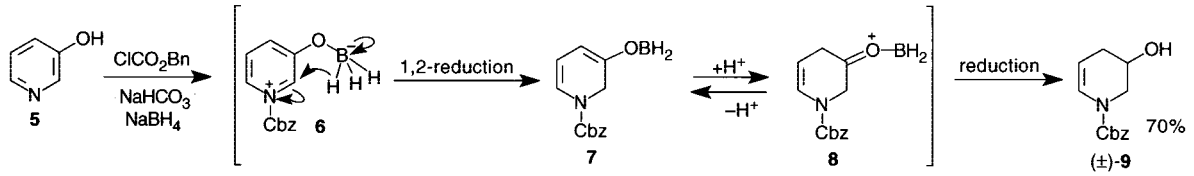
Scheme 1

Allylic alcohols, such as **2** and **4**, which are located on the piperidine ring system, have high potential as versatile intermediates for the construction of a variety of alkaloids. Their synthesis, however, is not an easy task as it took 10 and 8 steps, respectively, to obtain (±)-**2**[1] and (±)-**4**[2] from the readily available starting materials (Scheme 1). Therefore, development of an efficient procedure for the preparation of these compounds in enantiopure forms would have undoubtedly considerable synthetic merit. In this paper, we wish to report the synthesis of *N*-carbobenzoxy-3-hydroxy-1,2,3,6-tetrahydropyridine **9**, the structural isomer of **2**, in a single step[3a] from 3-hydroxypyridine **5**, its kinetic resolution[4] using lipase PS (*Pseudomonas* sp. Amano) and its transformation into **2** in enantiopure forms.[3b]

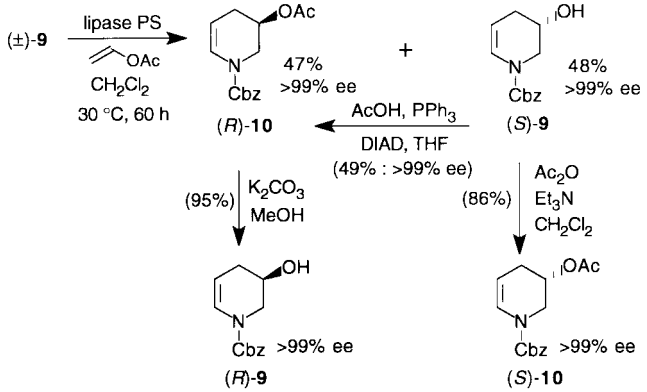
Since it has been reported[5] that reduction of pyridine with sodium borohydride in the presence of methyl chloroformate afforded *N*-carbomethoxy-1,2-dihydropyridine, we treated 3-hydroxypyridine **5** with sodium borohydride and carbobenzoxy chloride in the presence of sodium hydrogen carbonate in expectation of generating the *N*,*O*-dicarbobenzoxylated 1,2-dihydropyridine. Contrary to our expectation, the reaction proceeded in an unprecedented way to furnish *N*-carbobenzoxy-3-hydroxy-1,2,3,4-tetrahydropyridine (±)-**9** in 70% yield. The reaction was presumed to occur by initial formation of the carbobenzoxypyridinium boronate complex **6**, allowing regioselective reduction to give the 1,2-dihydro-intermediate **7** which, in turn, was isomerized to the ketone **8** and reduced to give rise to the final 1,2,3,4-tetrahydro-product (±)-**9** (Scheme 2).

Having discovered the unprecedented reductive carbamoylation of 3-hydroxypyridine **5**, we examined lipase-mediated resolution of the resulting cyclic homoallylic alcohol (±)-**9**. Thus, when (±)-**9** was stirred with vinyl acetate in dichloromethane in the presence of lipase PS at 30 °C, a clear-cut kinetic resolution occurred to give the (*R*)-acetate **10** in 47% yield leaving the (*S*)-alcohol **9** in 48% recovery yield, both with >99% ee. The latter was converted into the former in 49% yield without loss of the original chiral integrity by the Mitsunobu reaction[6] with acetic acid. The acetate (*R*)-**10** gave the alcohol (*R*)-**9** on alkaline methanolysis, while the alcohol (*S*)-**9** gave the acetate (*S*)-**10** under standard acetylation conditions (Scheme 3). The absolute configuration of the resolution products was determined[3b] by the conversion of the resolution product into (*R*)-4-amino-3-hydroxybutanoic acid[7,8] (GABOB), a hypotensive and antiseptic drug having the established structure.

Isomerization of the resolved alcohol **9** into the isomeric alcohol *N*-carbobenzoxy-3-hydroxy-1,2,3,6-tetrahydropyridine **2** was next examined. Since it was presumed that a 2,3-dihydropyridinium salt such as **13** may be an essential intermediate to give **2** by regiospecific 1,2-reduction, **9** was first treated with *N*-bromosuccinimide (NBS) to obtain the bromoacetal **11** to serve as the precursor of **13**. Upon treatment in methanol, (*R*)-**9** furnished the bromoacetal **11** regioselectively in 90% yield as a mixture of



Scheme 2



Scheme 3

epimers. Without separation, the mixture was refluxed with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in toluene to give the allyl acetal **12** which was treated with boron trifluoride, followed by sodium cyanoborohydride in tetrahydrofuran (THF) to accomplish concurrent formation of the iminium salt **13** and its specific 1,2-reduction to **2**.[9] Gratifyingly, the desired allyl alcohol (*S*)-**2** was obtained in 61% overall yield from the bromoacetal **11** under these conditions without loss of the original chiral integrity. The alcohol (*S*)-**2** thus obtained gave the acetate (*S*)-**14** under standard acetylation conditions (Scheme 4).

The racemic alcohol[1] (±)-**2** was also resolved under the same lipase-mediated conditions as mentioned above.[3c] Thus, treatment of (±)-**2** with vinyl acetate in dichloromethane in the presence of lipase PS afforded the acetate (*S*)-**14** in 47% yield leaving the alcohol (*R*)-**2** in 48% recovery yield, both with >99% ee. The former gave the alcohol (*S*)-**2** on alkaline methanolysis. On the other hand, the same alcohol (*S*)-**2** was also obtained from the enantiomeric alcohol (*R*)-**2** on Mitsunobu inversion using 4-nitrobenzoic acid[10] followed by methanolysis of the inverted benzoate product, but its enantiomeric purity was found to be somewhat decreased under these conditions (~89% ee) (Scheme 5).

In conclusion, the reduction of 3-hydroxypyridine with sodium borohydride in the presence of carbobenzoxy chloride was found to proceed in an unprecedented way to give rise to *N*-carbobenzoxy-3-hydroxy-1,2,3,4-tetrahydropyridine (±)-**9**. This was resolved under lipase-mediated trans-esterification conditions to give the (*R*)-acetate (*R*)-**10** leaving the (*S*)-alcohol (*S*)-**9,** both with >99% ee. The chiral alcohol (*R*)-**9** was transformed into the isomeric *N*-carbobenzoxy-3-hydroxy-1,2,3,4-tetrahydropyridine (*S*)-**2**, without loss of the original chiral integrity, which was also obtained from the racemic substrate (±)-**2** in enantiomerically pure forms employing the same lipase-mediated trans-esterification conditions.

Mps are uncorrected. IR spectra were recorded on a JASCO-IR-700 spectrometer. ^{1}H NMR spectra were recorded on a Gemini 2000 (300 MHz) spectrometer. Enantiomeric excess was determined on a Gilson Model-307 instrument equipped with a chiral column. Optical rotations were measured with a JASCO-DIP-370 digital polarimeter.

(±)-*N*-Carbobenzoxy-3-hydroxy-1,2,3,4-tetrahydropyridine (±)-9

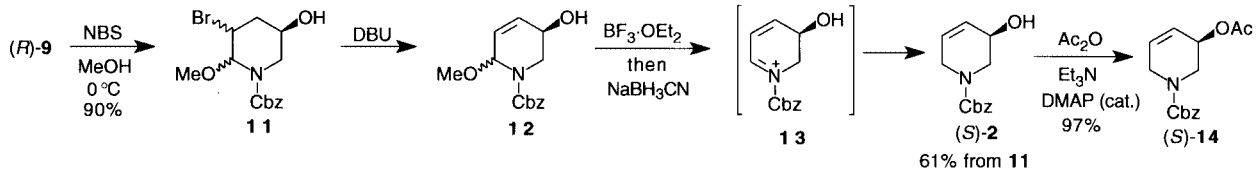
To a stirred suspension of 3-hydroxypyridine **5** (6.0 g, 61.8 mmol), $NaBH_4$ (5.1 g, 136.0 mmol) and $NaHCO_3$ (3.9 g, 46.4 mmol) in EtOH (250 mL) was added carbobenzoxy chloride (13.2 mL, 92.7 mmol), in portions, at −78 °C. The mixture was then stirred for 1.5 h at the same temperature. The reaction was quenched by addition of K_2CO_3 (1.0 g) at the same temperature. The mixture, after filtration through a Celite pad, was evaporated under reduced pressure, and the residue was extracted with EtOAc (2 × 300 mL). The extract was washed with brine (70 mL), dried ($MgSO_4$), evaporated under reduced pressure, and chromatographed (SiO_2, 500 g, EtOAc/hexane, 1:2) to give the homoallyl alcohol (±)-**9** (10.2 g, 70%) as a colorless oil.

IR (film): ν = 3400, 1704 cm^{-1}.

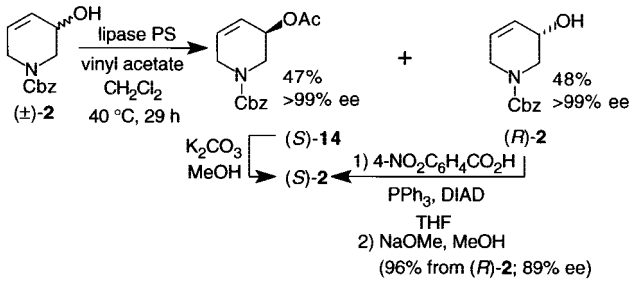
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.34 (s, 5H), 6.96−6.81 (m, 1H), 5.20 (s, 2H), 4.88−4.72 (m, 1H), 4.26−4.07 (m, 1H), 3.79−3.52 (m, 2H), 2.49−2.31 (m, 1H), 2.20−1.88 (m, 2H).

MS: *m/z* = 233 (M^+), 91 (100%).

HRMS: *m/z* calcd for $C_{13}H_{15}NO_3$ (M^+) 233.1052. Found: 233.1045.



Scheme 4



Scheme 5

Anal. Calcd for $C_{13}H_{15}NO_3$: C, 66.94; H, 6.48; N, 6.00. Found: C, 66.73; H, 6.52; N, 5.77.

Resolution of Racemic *N*-Carbobenzoxy-3-hydroxy-1,2,3,4-tetrahydropyridine (±)-9

A stirred mixture of the racemic alcohol (±)-**9** (6.25 g, 26.8 mmol), vinyl acetate (7.4 mL, 80.4 mmol) in CH_2Cl_2 (179 mL) was suspended with immobilized lipase, Lipase PS (*Pseudomonas* sp., Amano) (6.25 g), and the suspension was stirred at 30 °C for 60 h. The mixture, after filtration through a Celite pad, was evaporated under reduced pressure and chromatographed (SiO_2, 150 g, EtOAc/hexane, 1:2~4) to give the (*R*)-acetate **10** (3.49 g, 47%), $[\alpha]_D^{29}$ +13.0 (*c* 1.04, $CHCl_3$), as a colorless oil and the (*S*)-alcohol **9** (3.01 g, 48%), $[\alpha]_D^{27}$ +7.12 (*c* 0.96, $CHCl_3$), as a colorless oil. The enantiomeric excess of (*R*)-**10** was determined as 99% ee by HPLC using a column with a chiral stationary phase (CHIRALCEL OD, elution with 2% Pr^{i}OH/hexane: t_R = 38.8 min for (*R*)-**10** and 32.8 min for (*S*)-**10** at 0.5 mL/min). The enantiomeric excess of (*S*)-**9** was determined as >99% ee by HPLC as for (*R*)-**10** after transformation into the acetate (*S*)-**10**.

(*R*)-**10**: IR (film): ν = 1735, 1711 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.36 (s, 5H), 6.98−6.78 (m, 1H), 5.23−5.07 (m, 3H), 4.95−4.69 (m, 1H), 3.87−3.74 (m, 1H), 3.67−3.57 (m, 1H), 2.47−2.32 (m, 1H), 2.20−2.08 (m, 1H), 2.08−1.99 (m, 3H).

MS: *m/z* = 275 (M$^+$), 91 (100%).

HRMS: *m/z* calcd for $C_{15}H_{17}NO_4$ (M$^+$) 275.1156. Found: 275.1175.

Anal. Calcd for $C_{15}H_{17}NO_4$: C, 65.44; H, 6.22; N, 5.09. Found: C, 65.75; H, 6.37; N, 4.80.

Conversion of the Acetate (*R*)-10 into the Alcohol (*R*)-9

A solution of (*R*)-**10** (31 mg, 0.11 mmol) in MeOH (2 mL) was stirred with K_2CO_3 (80 mg, 0.57 mmol) at r.t. for 2 h. After evaporation of the solvent under reduced pressure the residue was diluted with EtOAc (40 mL) and the solution was washed with brine (5 mL), dried ($MgSO_4$), and evaporated under reduced pressure. The residue was chromatographed (SiO_2, 6 g, EtOAc/hexane, 1:2) to give the alcohol (*R*)-**9** (23.6 mg, 95%), $[\alpha]_D^{29}$ −7.14 (*c* 0.91, $CHCl_3$). Spectral data were identical to those of (*S*)-**9**.

Conversion of the Alcohol (*S*)-9 into the Acetate (*S*)-10

To a stirred solution of (*S*)-**9** (157 mg, 0.67 mmol) in CH_2Cl_2 (3.5 mL) were added Et_3N (0.34 mL, 2.41 mmol), 4-*N*,*N*-dimethylaminopyridine (DMAP) (2 mg, 0.01 mmol), and acetic anhydride (0.23 mL, 1.68 mmol) at 0 °C, and the mixture was stirred at r.t. for 40 min. The mixture was diluted with CH_2Cl_2 (30 mL) and was washed successively with 5% $NaHCO_3$ (5 mL) and brine (5 mL), dried ($MgSO_4$), evaporated under reduced pressure, and chromatographed (SiO_2, 10 g, EtOAc/hexane, 1:2) to give the acetate (*S*)-**10** (158 mg, 86%), $[\alpha]_D^{29}$ −13.0 (*c* 1.04, $CHCl_3$), as a colorless oil.

Conversion of the Alcohol (*S*)-9 into the Inverted Acetate (*R*)-10

To a stirred solution of (*S*)-**9** (99% ee) (228 mg, 0.98 mmol) in THF (5 mL) were added Ph_3P (334 mg, 1.27 mmol), diisopropyl azodicarboxylate (DIAD) (0.25 mL, 1.27 mmol) and HOAc (0.07 mL, 1.27 mmol) at 0 °C. After stirring at r.t. for 3 h, the mixture was evaporated under reduced pressure, and the residue was chromatographed (SiO_2, 100 g, EtOAc/hexane, 1:4) to give the acetate (*R*)-**10** (132 mg, 49%), $[\alpha]_D^{29}$ +13.8 (*c* 0.93, $CHCl_3$). Spectral data were identical to those of (*S*)-**10**. Enantiomeric excess was determined as 99% ee by HPLC using a column with a chiral stationary phase (CHIRALCEL OD, 2% Pr^{i}OH/hexane).

***N*-Benzoxy-3-bromo-5-hydroxy-2-methoxypiperidine 11**

To a stirred solution of alcohol (*R*)-**9** (7.7 g, 33.0 mmol) in MeOH (170 mL) was added *N*-bromosuccinimide (NBS) (6.5 g, 36.4 mmol) at 0 °C and the mixture was stirred at the same temperature for 1 h. The mixture was washed successively with 5% $NaHCO_3$ (50 mL) and 10% $Na_2S_2O_3$ (50 mL), dried ($MgSO_4$), and chromatographed (SiO_2, 70 g, EtOAc/hexane, 1:2) to give the bromo-ether **11** (10.2 g, 90%) as a colorless oil, as a diastereomeric mixture.

IR (film): ν = 3456, 1684 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.35 (s, 5H), 5.87−4.96 (m, 4H), 4.54−3.82 (m, 3H), 3.46−3.05 (m, 3H), 2.95−1.88 (m, 3H).

MS: *m/z* = 343 (M$^+$), 312 (M$^+$−31), 91 (100%).

HRMS: *m/z* calcd for $C_{14}H_{18}BrNO_4$ (M$^+$) 343.0419. Found: 343.0417.

Anal. Calcd for $C_{14}H_{18}BrNO_4$: C, 48.85; H, 5.27; N, 4.07; Br, 23.31. Found: C, 49.00; H, 5.33; N, 3.97; Br, 23.23.

(*S*)-*N*-Carbobenzoxy-3-hydroxy-1,2,3,6-tetrahydropyridine (*S*)-2

A mixture of the bromo-ether **11** (2.9 g, 8.43 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (2.5 mL, 16.9 mmol) in toluene (17 mL) was refluxed for 12 h. After cooling, the mixture was diluted with Et_2O (200 mL) and then washed successively with H_2O (50 mL) and brine (50 mL), dried ($MgSO_4$) and evaporated under reduced pressure.

The residue containing the allyl alcohol **12** was then dissolved in THF (52 mL) and the solution was treated with BF_3•OEt_2 (1.9 mL, 15.5 mol) and $NaBH_3CN$ (974 mg, 15.5 mmol) at 0 °C with stirring. After 30 min, the mixture was made basic by addition of 5% $NaHCO_3$ (50 mL) and extracted with EtOAc (2 × 100 mL). The extract was washed with brine (50 mL), dried ($MgSO_4$), evaporated under reduced pressure, and chromatographed (SiO_2, 70 g, EtOAc/hexane, 1:2) to give the allyl alcohol (*S*)-**2** (1.2 g, 61%), $[\alpha]_D^{30}$ −67.0 (*c* 0.96, $CHCl_3$), as a colorless oil. The enantiomeric excess of (*S*)-**2** was determined as 99% ee by HPLC using a column with a chiral stationary phase (CHIRALCEL OD, elution with 10% Pr^i-OH-hexane).

IR (film): ν = 3414, 1698 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.31 (s, 5H), 5.99−5.73 (m, 2H), 5.16 (s, 2H), 4.33−3.97 (m, 2H), 3.96−3.78 (m, 1H), 3.78−3.50 (m, 2H), 2.02 (m, 1H).

MS: *m/z* = 233 (M$^+$), 91 (100%).

HRMS: *m/z* calcd for $C_{13}H_{15}NO_3$ (M$^+$) 233.1051. Found: 233.1048.

Conversion of the Alcohol (*S*)-2 into the Acetate (*S*)-14

To a stirred solution of (*S*)-**2** (63 mg, 0.27 mmol) in CH_2Cl_2 (2 mL) were added Et_3N (0.14 mL, 0.97 mmol), 4-*N*,*N*-dimethylaminopyridine (2 mg, 0.01 mmol), and acetic anhydride (0.06 mL, 0.68 mmol) at 0 °C, and the mixture was stirred at r.t. for 1 h. The mixture was diluted with CH_2Cl_2 (40 mL) and was washed successively with 5% $NaHCO_3$ (10 mL) and brine (10 mL), dried ($MgSO_4$),

evaporated under reduced pressure, and chromatographed (SiO_2, 10 g, EtOAc/hexane, 1:4) to give the acetate (*S*)-**14** (72 mg, 97%), $[\alpha]_D^{29}$ −114.8 (*c* 1.00, $CHCl_3$).

IR (film): ν = 1695 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.47 (s, 5H), 6.60−5.82 (m, 2H), 5.29−5.05 (m, 2H), 4.32−4.14 (m, 1H), 3.96−3.78 (m, 2H), 3.59−3.48 (dd, 1H, *J* = 13.9, 4.0 Hz), 2.07−1.93 (m, 3H).

MS: *m/z* = 215 (M^+-50), 91 (100%).

HRMS: *m/z* calcd for $C_{13}H_{13}NO_2$ (M^+) 215.0946. Found: 215.0939.

Anal. Calcd for $C_{15}H_{17}NO_4$: C, 65.44; H, 6.22; N, 5.09. Found: C, 65.28; H, 6.09; N, 5.11.

Resolution of Racemic *N*-Carbobenzoxy-3-hydroxy-1,2,3,6-tetrahydropyridine (±)-2

A stirred mixture of the racemic alcohol (±)-**2** (1.68 g, 7.21 mmol), vinyl acetate (3.3 mL, 35.8 mmol) in CH_2Cl_2 (80 mL) was suspended with immobilized lipase, Lipase PS (*Pseudomonas* sp., Amano) (1.62 g), and the suspension was stirred at 40 °C for 29 h. The mixture, after filtration through a Celite pad, was evaporated under reduced pressure and chromatographed (SiO_2, 150 g, EtOAc/hexane, 1:3~1) to give the acetate (*S*)-**14** (921 mg, 46.5%), $[\alpha]_D^{30}$ −115.5 (*c* 0.96, $CHCl_3$), as a colorless oil, and the alcohol (*R*)-**2** (800 mg, 47.6%), $[\alpha]_D^{27}$+65.9 (*c* 0.87, $CHCl_3$), as a colorless oil. Spectral data of the products were identical to those of (*S*)-**2** and (*S*)-**14**, respectively.

The enantiomeric excess of the acetate (*S*)-**14** was determined as 99% ee by HPLC using a column with a chiral stationary phase (CHIRALCEL OD, 10% Pr^iOH/hexane: t_R = 20.5 min for (*S*)-**2** and 28.3 min for (*R*)-**2** at 0.5 mL/min) after transformation into the alcohol (*S*)-**2** by methanolysis.

The enantiomeric excess of the alcohol (*R*)-**2** was determined as >99% ee by HPLC using a column with a chiral stationary phase (CHIRALCEL OD, elution with 10% Pr^iOH/hexane).

Conversion of the Acetate (*S*)-14 into the Alcohol (*S*)-2

A solution of (*S*)-**14** (1.26 g, 4.36 mmol) in MeOH (15 mL) was stirred with K_2CO_3 (903 mg, 6.54 mmol) at r.t. for 1.75 h., and the mixture, after filtration through a Celite pad, was evaporated under reduced pressure. The residue was diluted with EtOAc (100 mL) and the solution was washed with brine (30 mL), dried ($MgSO_4$), and evaporated under reduced pressure. The residue was chromatographed (SiO_2, 30 g, EtOAc/hexane, 1:2) to give the alcohol (*S*)-**2** (990 mg, 97%), $[\alpha]_D^{27}$ −67.0 (*c* 0.9, $CHCl_3$). The spectral data were identical to those of (*R*)-**2**.

Inversion of the Alcohol (*R*)-2 into the Enantiomer (*S*)-2

To a stirred solution of (*R*)-**2** (>99% ee) (49 mg, 0.21 mmol) in THF (2 mL) were added Ph_3P (66 mg, 0.25 mmol), DIAD (0.04 mL, 0.25 mmol), and 4-nitrobenzoic acid (0.07 mL, 1.27 mmol) at 0 °C. After stirring at r.t. for 30 min, the mixture was evaporated under reduced pressure and the residue was chromatographed (SiO_2, 20 g, EtOAc/hexane, 1:3) to give the crude benzoate (110 mg) as a pale yellow oil.

The crude benzoate was dissolved in MeOH (2 mL) containing sodium methoxide, prepared in situ from Na (15 mg, 0.63 mol) in the same flask, at 0 °C and stirred at r.t. for 20 min. After quenching the reaction by addition of 5% $NaHCO_3$ (20 mL), the mixture was extracted with CH_2Cl_2 (40 mL). The extract was washed with brine, dried ($MgSO_4$), evaporated under reduced pressure, and chromatographed (SiO_2, 30 g, EtOAc/hexane, 1:2) to give (*S*)-**2** (47 mg, 96% in 2 steps) as a colorless oil. The spectral data were identical with those of (*R*)-**2**, but enantiomeric excess was determined as 89.4% ee by HPLC using a column with a chiral stationary phase (CHIRALCEL OD, 10% Pr^iOH/hexane).

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